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THE ETIOLOGY OF DIPHTHERIA.

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THE ETIOLOGY OF DIPHTHERIA.[1]

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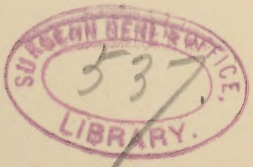
OF the infectious diseases there is scarcely one that has passed through as interesting and as remarkable a history as diphtheria. Numerous investigators attempted, at quite an early date, to throw light upon the cause of this dreadful disease. Their efforts, however, were largely unsuccessful, owing to the extreme difficulties presenting themselves at that early period in the study of bacterial affections. In the normal individual the mouth harbors a large number of micro-organisms, and in diseases of the mouth or throat the number and kind of micro-organisms are still further increased. No wonder, then, that this abundant and luxuriant flora of the mouth served to divert and nonplus the early pioneers in this important study.

One thing, however, was certain, namely, that the cause of diphtheria was a microbe—a living organism. It is only too well known that diphtheria is a communicable disease, that it is transmissible from one individual to another. This fact can be explained in but one way, and that is that a living organism is transmitted from one person to another.

[1] Read before the Michigan State Medical Society, June 5, 1895.



The attribute of life is essential to the cause of an infectious disease, and diphtheria certainly occupies a front rank in this class.

Our present knowledge regarding the microbic cause of diphtheria may be said to begin in 1883, when Klebs found, by microscopic examination of a number of cases of diphtheria, the bacillus that today is known throughout the world as the cause of diphtheria. During the following year Loeffler succeeded in isolating the bacillus in absolutely pure culture. He was therefore able to describe minutely its morphologic, tinctorial, cultural, and biologic properties, and by so doing furnished a firm, permanent, reliable foundation on which subsequent workers could build with that confidence which has brought about one of the greatest achievements in medicine.

Loeffler confirmed the observations of Klebs regarding the presence of this bacillus in the false membranes of this disease. In twenty-seven diphtheric membranes examined he found the bacillus present in about one-half. On the other hand, in some of the sections examined the bacillus could not be found—a failure due undoubtedly, as he himself points out in 1890, to the fact that some of the early cases studied were not typical cases of diphtheria. Between 1884 and 1890 he examined twenty-one fresh cases of diphtheria, and in every one of these the characteristic bacillus was demonstrated. Inoculations with pure cultures of this bacillus into the trachea of rabbits, guinea-pigs, chickens, and doves produced a croupous-like condition, due to the formation of false membranes.

Similar results were obtained by vaginal inoculations in guinea-pigs, and also by applications to the conjunctiva and pharynx. When injected subcutaneously into guinea-pigs a hemorrhagic edema with grayish-white exudate formed.

The fact that the bacilli were always found in guinea-pigs at the point of inoculation, and not within the organs, led Loeffler to conclude that the microorganisms produced a powerful poison which was absorbed and carried throughout the body. This view was subsequently established by Loeffler's own researches in 1887 and 1888 on the poisonous products of the bacillus, and, above all, by the classic researches of Roux and Yersin in 1888 and of Brieger and Fraenkel in 1890.

Notwithstanding the frequent presence of this bacillus in the disease, and the diphtheria-like results obtained by inoculating animals with pure cultures of the bacillus, Loeffler, with characteristic modesty and reserve, with the true spirit of a scientific investigator, refrained from designating it as the cause of diphtheria. This hesitation was due to several reasons. In the first place, he had found the same bacillus, identical morphologically and physiologically, in the mouth of a healthy child. Again, the typical diphtheric paralyses observed in man were not reproduced in animals; also, when applied to the uninjured mucous membranes of animals, the cultures had no effect. Furthermore, as already stated, the bacillus was not always found in the sections of membranes examined; and, lastly, the bacilli showed a different arrangement in the false membranes from animals compared with those

from man. In view of these facts, Loeffler came to the conclusion that, while the bacillus was probably the cause of diphtheria, more investigation would be necessary to prove this relationship definitely.

The doubt expressed by Loeffler as to the relation of the bacillus to diphtheria unquestionably contributed to discourage other investigators, for during the next three years practically no further studies were made. In his second paper, in 1887, Loeffler pointed out the constant presence of the germ in ten cases, and at the same time discovered the pseudo-diphtheria-bacillus, which differed from the bacillus first studied, in addition to slight morphologic and cultural differences, in the absence of any pathogenic power with respect to guinea-pigs.

In the following year Hofmann, whose untimely and tragic death will ever remain in the memory of bacteriologists, studied the occurrence of the Klebs-Loeffler bacillus in diphtheria. He succeeded in finding the bacillus in six out of eight cases, but he failed to establish any specific relation between the bacillus and the disease, for much the same reasons that led Loeffler to question the correctness of his own interpretations. Thus Hofmann met with the non-pathogenic, pseudo-diphtheria-bacillus in diphtheric membranes and also in twenty-six out of forty-five diseased but not diphtheric mucous membranes. He likewise demonstrated a marked variation in the virulence of the Loeffler bacillus obtained from different cases, and from old cultures. Furthermore, the virulent bacillus was found in a case of measles, and in one individual out of eleven in whom no throat-complication existed.

In December, 1888, Roux and Yersin published their first memoir on diphtheria, in which they were able to take the definite stand that the Klebs-Loeffler bacillus was the specific cause of diphtheria. They considered themselves justified in taking this position because: (1) they found the Loeffler bacillus present in each one of the fifteen cases of diphtheria examined; (2) by means of pure cultures of the bacillus they reproduced false membranes in animals, just as Loeffler had done; (3) they succeeded with pure cultures in producing paralyses in animals similar to the post-diphtheric paralyses in man; (4) they demonstrated that the bacillus gives rise to poisonous products which, when injected into animals, produced either death or paralyses, according to the dose. This publication of Roux and Yersin attracted widespread attention, and led numerous workers to take up the subject of the etiology of diphtheria. The result of these investigations was the confirmation of Roux and Yersin's conclusions, and, with this achievement once accomplished, it became possible for Behring to enter definitely upon that research which has given, and will give, invaluable benefits to mankind.

Let us consider now, in a somewhat general way, the evidence that has been brought forward during the past ten years regarding the etiology of diphtheria. In the first place, in order that a microorganism shall be considered as the cause of a disease, the requirement is exacted that it shall be found in every case of that disease. This so-called first rule of Koch, framed at a very early period in the history of the etiology of infectious diseases,

assumes some things that, in the light of our present knowledge of the *rôle* of micro-organisms in infection, cannot be disregarded. Thus, that which for clinical or anatomic reasons is described as a definite disease may in reality be far from being an entirety. A rational or natural classification in general biologic science is based upon natural, intimate relationships, and not upon mere appearance or form. The division of diseases by the clinician, based on mere clinical observations, or by the pathologic anatomist, based on anatomic relations, are largely classifications of convenience, and in no wise bring out the relation that is closest and most intimate to the disease—that of the cause. It does not require much reasoning to show that what is clinically or anatomically designated as a disease may have only one cause or may have several distinct causes. In the latter case, what was called a disease becomes, through the study of its etiology, a group of diseases. The old typhoid fever has passed through such a history, and we may say in advance that diphtheria has recently experienced a similar development.

We may now ask ourselves, Is the Loeffler bacillus present in every case of diphtheria? Is the first rule of Koch demonstrated? From the earliest investigations of Klebs in 1883, and of Loeffler in 1884, until the present day, it is evident that the Loeffler bacillus is present in a very large proportion of the cases of clinical diphtheria. In the following table an effort is made to compile all available reports of bacteriologic examinations, from outside the United States, of diphtheria, made in ten cases or more,

showing the number of cases examined and the number of times the Loeffler bacillus has been found :

	No. of cases examined.	No. of times Loeffler bacillus found.		No. of cases examined.	No. of time: Loeffler bacillus found.
Sörensen, 1886	10	7	Baginsky, 1892	154	118
Roux & Yersin, 1888	15	15	Hoppe-Seyler, 1892	37	23
Kolisko & Paltauf, 1889	about 50	In nearly all.	Loeffler & Strübing, 1894	100	75
Ortmann, 1889	16	15	Plaut, 1894	80	22
Zarniko, 1889	20	18	Ritter, 1894	225	225
Babes, 1890	42	42	Phillip—Baginsky, 1894	333	332
Brieger & Froenkel, 1890	22	22	Chaillou & Martin, 1894	198	155
Beck, 1890	53	52	Roux, Chaillou, and Martin, 1894	448	320
D'Espine, 1890	15	11	Feer, 1894	44	38
Escherich, 1890	22	20	Kossel, 1894	117	117
Klein, 1890	22	22	Katz, 1894	128	128
Loeffler, 1890	21	21	Hilbert, 1894	11	11
Roux & Yersin, 1890	80	61	Bernheim, 1894	12	11
Spronck, 1890	13	13	Bergmann, 1894	46	46
Morel, 1891	86	96	Schmorl, 1894	10	7
Pletzer, 1891	12	7	Fraenkel, 1895	about 100	in all but few.
Concetti, 1892	21	16			
Heubner, 1892	113	77			
Janson, 1893	83	63			
Martin, 1892	200	137			
Sakharoff, 1892	19	13		2846	2344
Tangl, 1892	18	18	Percentage,	.....	82.4

From this table it will be seen that in 2846 cases examined by European workers the Loeffler bacillus was met with 2344 times, or 82.4 per cent. The result is somewhat higher than that obtained by American investigators, who, it will be observed, largely through the efficient support of the Board of Health of the City of New York, examined nearly twice as many cases as given in the preceding table.

	No. of cases examined.	No. of times Loeffler bacillus found.
Park, 1892	140	54
Park, 1893	104	73
Park and Beebe, 1894 . . .	4795	3255
Morse, 1894	301	217
	5340	3599
Percentage . .	.....	67.5

If we now combine the results obtained by American and European workers, we shall have 8186 cases, in which the Loeffler bacillus was found 5943 times, or in 72.6 per cent. of the cases.

These two tables contain the results obtained by a large number of investigators, in different laboratories and in different countries, employing at times methods more or less different. In many instances, the cases examined are described as suspicious or very suspicious. The degree of suspicion, as Welch has pointed out, is a relative one, depending on the physician, for when one physician considers a case to be highly suspicious, another may regard it as very doubtful. Accurate, positive clinical diagnosis of diphtheria in many of the foregoing cases is lacking, and the low percentage that these statistics furnish may in part at least be explained by this dilution with suspicious cases. For purposes of diagnosis, of course, the examination of suspicious cases is extremely valuable, but in statistics intended to show the frequency of the Loeffler bacillus in diphtheria they can have but one effect, that of lowering the percentage. This is true in the two tables already given and in the third table which serves as an excellent comparison with the work of the American

bacteriologists, giving the results obtained by the French investigators of the Pasteur Institute of Paris.

These results, it will be observed, are obtained by men working in the same laboratory, employing the same methods of research, and studying cases in one and the same hospital. These figures are already included in the first table. It will be seen from this table that the Loeffler bacillus was found in 73 per cent., which coincides closely with the percentage-frequency in all cases examined. Bearing in mind that these French bacteriologists are all skilled workers, it will be evident that this percentage is low because of errors in diagnosis by the internes of the hospital.

	No. of cases examined.	No. of times Loeffler bacillus found.
Roux and Yersin, 1888 . . .	15	15
Roux and Yersin, 1890 . . .	80	61
Martin, 1892	200	137
Sakharoff, 1892	19	13
Chaillou and Martin, 1894 . .	198	155
Roux, Chaillou, and Martin, 1894	448	320
	960	701
Percentage		73

The available statistics then show that 73 per cent. of all clinical and suspicious cases of diphtheria contain the Loeffler bacillus. That this percentage will be higher when greater care is taken in diagnosis, excluding suspicious or doubtful cases, is evident. Furthermore, there are other conditions that bear upon the detection of a given micro-organism in disease, and all of these factors tend to lower the percentage. Thus, in the first place, the accuracy and skill of the individual in detecting the Loeffler bacil-

lus are to be considered. The more experience one has in this kind of work, the more easily and frequently will the bacillus be found. Again, much will depend on the method of staining and on the method of cultivation. Certain stains are preferable to others, and the same is true of the medium on which the germ grows. Again, failure of detection may result from conditions over which the bacteriologist has no control. Thus, the material which is removed from the throat may not be from that portion where the Loeffler bacillus is present. Mere touching or scraping of the surface of the membrane does not necessarily carry with it the bacillus, which may, however, be present in the membrane. Again, the Loeffler bacillus may be present, but outgrown by the large number of foreign germs that may be present. In such cases the detection of the germ becomes a mere accident. Further, the bacillus may be inhibited or even prevented in its growth on culture-media by a previous application of antiseptics to the throat. That such cases may and do occur has been shown recently by Plaut.

There is reason, therefore, to believe that the percentage of cases of diphtheria in which the Loeffler bacillus exists is greater than that given in the preceding statistics. With proper care in diagnosis and in the removal of portions of membrane from the throat, supplemented by skilled investigators using reliable, well-tried methods, the percentage of cases in which the Loeffler bacillus is found may rise to a marked extent, as seen from the following table.

	No. of cases examined.	No. of times Loeffler bacillus found.
Phillips (Baginsky)	333	332
Bernheim	12	11
Hilbert	11	11
Katz	128	128
Kossel	117	117
Loeffler and Strübing	100	75
Ritter	225	225
Bergmann	46	46
Fraenkel	about 100	in all but few
	972	945
Percentage	.....	97.2

These figures are already included in the first table. They were all obtained during the past year (1894) by German workers. Plaut's results are omitted because most of his cases were diagnosticated as "suspicious" or "very suspicious."

In connection with the presence of the Loeffler bacillus in diphtheria it should be emphasized, contrary to Hansemann, that there are cases in which the bacillus is present in perfectly pure culture, unaccompanied by any other germ. This is especially true if the examination be made at an early stage, as has been demonstrated by Martin, by Chaillou and Martin, by Fraenkel, and by others. Subsequently, as the disease progresses, other bacteria, especially cocci, make their appearance, and may not only outnumber but even suppress the Loeffler bacillus.

These bacteriologic studies with reference to the frequency of the Loeffler bacillus in diphtheria demonstrate clearly that this bacillus is present in more than the 75 percentage of all cases of real clinical diphtheria, as stated by Loeffler and conceded even by Hansemann. There remain, however, still a sufficiently large percentage of clinical diphtherias

from which the Loeffler bacillus is unquestionably absent. In these cases, which, in many respects, are undistinguishable clinically from those in which the Loeffler bacillus is present, other micro-organisms are found. These forms of diphtheria may be due to several other micro-organisms, as has been shown by Roux, Chaillou, and Martin in their researches. They cannot be said to be proved to be causes of such diphtherias, but, nevertheless, there is much reason to believe that such is the case.

The French bacteriologists divide anginas into two groups: First, diphtheric anginas, those in which the Loeffler bacillus is present; and, second, non-diphtheric anginas, those in which it is absent and which, as stated, are undoubtedly due to other micro-organisms, above all to cocci. Thus in 112 anginas examined by Martin, 69 were found to be diphtheric and 43 non-diphtheric. The most common organism found in the latter group in 25 cases was a coccus. The next most common organism was the streptococcus, found in 8 cases, and in a few others the staphylococcus albus, aureus, and other cocci predominated.

In a second series by Chaillou and Martin, 99 anginas were examined, and 70 were found to be diphtheric and 29 non-diphtheric. Of the latter, 11 had the small coccus of Brisou, 11 had streptococci, and 4 had staphylococci. In the 448 cases examined last year by Roux, Chaillou, and Martin, 128 were found to be non-diphtheric. The study of croup by these same observers has likewise demonstrated that all croups are not diphtheric. They may likewise be divided into diphtheric and non-

diphtheric croups. The latter, as in the case of the anginas, may be due to the Brisou coccus, the streptococcus, the staphylococcus, and other organisms. As seen from the subjoined table, the number of non-diphtheric croups is much less—nearly one-half—than the non-diphtheric anginas:

Anginas:	No. of cases.	Diphtheric	Non-diphtheric.
Martin . . .	112	69	43
Chaillou and Martin	99	70	29
	211	139	72
Percentage . .	....	.....	**34.1**
Croups:			
Martin . . .	88	68	20
Chaillou and Martin	99	85	14
	187	153	34
Percentage . .	...	...	**18.2**

The bacteriologic examinations show clearly, therefore, that diphtheria, as it is commonly understood, may be due to several causes—in other words, that we have a group of diseases that clinically often cannot be distinguished, but that, nevertheless, are etiologically different. It has been proposed to designate those cases in which the Loeffler bacillus is present as true diphtheria, or bacillar diphtheria, or diphtheria, for short; while those cases in which it is not present are spoken of as false diphtheria or pseudo-diphtheria, coccus-diphtheria, or diphtheroid.

Inasmuch as those cases in which the Loeffler bacillus is present are most numerous and most fatal, this form of diphtheria above all requires our attention. What evidence do we possess, then, that the Loeffler bacillus is actually the cause of those cases of diphtheria in which it occurs?

In order to prove this relationship it is necessary to obtain the bacillus in perfectly pure culture, free from all other micro-organisms. This can readily be accomplished, thus satisfying the second rule of Koch. The pure cultures thus obtained, when inoculated into susceptible animals, must now produce the same disease, with all its symptoms and pathologic changes, and in the animal thus artificially infected the germ is to be found distributed the same as in the natural case. This severe requirement is rarely complied with, for the reason that the animals which are used for experimentation, while susceptible to the action of the germ, can scarcely be expected to reproduce all the details of the disease as it exists in man. Thus the bacillus of glanders, which has been shown to be the cause of glanders in the horse, producing in that animal typical glanders, will, if inoculated into a field-mouse, produce death, but without the slightest resemblance to the disease in the horse. In other animals, as the guinea-pig, the bacillus does produce effects strikingly like those of glanders. Other instances might be cited to show that when experimenting with bacteria on animals other than those in which the disease naturally occurs, variations are met with and must be expected. What, then, is the effect of the Loeffler bacillus when inoculated into susceptible animals?

Fortunately, the results obtained by such inoculations are so striking and bear so great a resemblance to the natural disease in man as to leave no doubt in the minds of those who are at all familiar with the work that has been done in this direction. The

production of experimental diphtheria in animals by Loeffler, and above all by Roux and Yersin, is in itself sufficient to show that the Loeffler bacillus is the cause of diphtheria. Guinea-pigs, pigeons, and rabbits are most susceptible to the Loeffler bacillus. Subcutaneous injections of a virulent culture into these animals almost invariably produce death in from twenty-four to forty-eight hours. A more or less extended gelatinous edema forms at the point of inoculation; a grayish pseudo-membrane forms and the glands are enlarged. Serous effusions in the pleura are common in the guinea-pig, but very rare in rabbits. On the other hand, the liver in guinea-pigs is apparently unaffected, whereas in the rabbit fatty degeneration takes place. The inoculations on the mucous surfaces are especially characteristic. In order to succeed, the mucous membrane must first be slightly injured; otherwise infection does not result. Inoculations in the pharynx, trachea, conjunctiva, and vulva of animals are followed by the formation of false membranes, general intoxication, and death. In tracheal inoculations the false membranes may spread, as Fraenkel points out, covering the entire walls of the air-passages even as far as the large bronchi. The tissues are edematous and the glands swollen. A more striking resemblance to the natural disease can hardly be expected in animals that are not naturally susceptible to the disease.

The post-diphtheric paralyses observed in man have also been reproduced in animals by Roux and Yersin, Brieger and Fraenkel, and others. These paralyses are especially well marked in pigeons,

rabbits, and dogs that have been inoculated with a quantity of the germ insufficient to kill in a short time. In from six days to two or three weeks from the inoculation typical paralyses develop and the animal either recovers or eventually dies. The production of false membranes on mucous surfaces and subsequent paralyses in animals complete the resemblance to the natural disease to such an extent as to establish the specific relation of the Loeffler bacillus to diphtheria.

Not only can pure cultures of the bacillus cause the paralyses in animals, but the chemic products of the bacillus can accomplish the same result. The researches of Roux and Yersin on the poison produced by the Loeffler bacillus mark a new era in the study of diphtheria. The filtered, germ-free cultures of the Loeffler bacillus, when injected into rabbits in doses not sufficient to kill in a short time, produce typical paralyses. That similar poisons are elaborated in the body of diphtheria-patients has been demonstrated by these investigators and by others. Thus, the spleen and urine of a child dead of diphtheria were shown to contain the same or similar poisons that, when injected into a rabbit, were followed by prolonged paralysis and death.

The effect of pure cultures of the Loeffler bacillus and of its chemic products on animals may be said to establish its relation to diphtheria. There are, however, two other facts that still further emphasize this relation. In the first place, the high mortality of those cases of diphtheria in which the Loeffler bacillus is present is in striking contrast with the mortality of those cases in which it is absent.

This is no accident, much less a myth, as Hansemann would believe.

In the 80 cases studied by Roux and Yersin in 1890, the Loeffler bacillus was present in 61 cases and absent from 19. All of these 19 recovered, whereas of the 61 cases in which the bacillus was present 30 died. Again, of the 200 cases examined by Martin in 1892, the Loeffler bacillus was found in 137 cases and was absent from 63 cases. Of 55 non-diphtheric anginas and croup 7 died; 4 of these, however, became infected with the Loeffler bacillus in the hospital, subsequent to tracheotomy, and 1 died of broncho-pneumonia. Of 137 diphtheric anginas and croups 72 died. The study of the 198 cases presented by Chaillou and Martin in 1894 develops the same remarkable difference in the mortality of the two groups. Thus, in the 198 cases of angina and croup mentioned, the Loeffler bacillus was found 155 times and was absent from 43 cases. Of the 43 non-diphtheric cases 4 died, 3 of these as a result of subsequent infection in the hospital with the Loeffler bacillus. Of the 155 cases in which the Loeffler bacillus was present 83 died. Again, of the 448 cases reported on by Roux and his coworkers last year, treated with serum, 109 died; 320 of these cases had the Loeffler bacillus, and gave a mortality of 98; 128 did not have the Loeffler bacillus, and gave a mortality of 11.

These figures are brought together in the following table, and furnish an interesting subject for study:

	No. of cases with Loeffler bacillus.	Deaths.	Per cent.	No. of cases without Loeffler bacillus.	Deaths.	Per cent.
Roux and Yersin . . .	61	30	**49.2**	19	0	0
Martin	137	72	**52.6**	55	7	**12.7**
Chaillou and Martin . .	155	83	**53.5**	43	4	9.3
Average . . .	353	185	**52.4**	117	11	**9.4**
Antitoxic serum; Roux, Chaillou, and Martin	300	78	**26.0**	128	11	**8.6**

The bacteriologic examination of clinical diphtheria, therefore, shows clearly that the mortality in those cases in which the Loeffler bacillus is present is about 50 per cent. On the other hand, those forms that are clinically undistinguishable from the preceding, but do not contain the Loeffler bacillus, possess a mortality of 10 per cent., which, however, includes those that died of subsequent infection with the Loeffler bacillus. Deducting these, assuming that all would recover, the mortality would sink to less than 4 per cent. Certainly no more remarkable evidence of the etiologic relation of the Loeffler bacillus to diphtheria can be presented than that shown from the study of the relative mortalities.

As a final proof of the relation of the Loeffler bacillus to diphtheria, we will mention in a general way the results obtained from the use of the antitoxic serum. First of all, it is desirable to emphasize the experimental fact that the serum of animals rendered arti-

ficially immune to the diphtheria-bacillus or its products will protect absolutely animals against many times the fatal dose of the diphtheria-bacillus or of its poison. This fact is as well established by direct experimentation on animals as the chemic fact that sodium hydroxid and hydrochloric acid neutralize each other. Secondly, it will be remembered that in diphtherias in which the Loeffler bacillus is present, poisons the same as those formed in pure cultures are produced and can be found in the organs, as has been done by Roux and Yersin and others. The antitoxic serum that protects animals against infection with the Loeffler bacillus must likewise protect the person afflicted with diphtheria due to the Loeffler bacillus. That it actually does protect is abundantly demonstrated by treatment of diphtheria during the past year.

To emphasize the statement already made, it will be sufficient to present one or two instances. Of the 300 cases treated with the antitoxic serum and reported on by Roux, at Budapest, last September, only 78 died, giving a mortality of 26 per cent. These results were obtained in the same hospital in which Chaillou and Martin established the fact that in diphtheria in which the Loeffler bacillus is present the mortality is above 50 per cent.

Furthermore, showing the specific action of the antitoxic serum on the Loeffler bacillus and its products, it will be seen, from results already cited, that in 128 non-diphtheric cases treated the mortality was 8.6 per cent. against 9.4 per cent. in non-treated cases. The serum is, therefore, without any effect in cases in which the Loeffler bacillus is not present,

and in those cases in which it was present the mortality was reduced by one-half, that is, 25 per cent. were saved. Since then the mortality-record has been lowered considerably. Thus, in 128 cases of diphtheria containing the Loeffler bacillus, treated by Katz, only 17 died, giving a mortality of 13.2 per cent.; 117 cases treated by Kossel gave 13 deaths, a mortality of 11.1 per cent.

Because the protection against the Loeffler bacillus is absolute in animals, it must not be expected that similar results will be obtained in man. A certain mortality will necessarily exist, owing to conditions over which the physician can have no control. In experiments on animals, three factors are involved : the animal body, the Loeffler bacillus or its poison, and the antitoxic serum. It is well known from experiments that an animal cannot be saved when the duration of the disease or of the intoxication has been too long. Irreparable injury has already been done. The same results must, therefore, be expected in the human subject when the disease has progressed beyond a certain point.

Furthermore, in the human subject, in addition to the three factors mentioned, another one is to be considered, and that is the association of the Loeffler bacillus with other micro-organisms. It is to-day a well established fact in bacteriology that a given pathogenic germ may be favored or retarded in its action by the presence of other organisms. In diphtheria, both of these conditions are not infrequently met. Roux and Yersin have shown that the virulence of the Loeffler bacillus, with respect to animals, is increased by associating it with the streptococcus

of erysipelas. The statistics furnished by Chaillou and Martin are especially valuable in this regard. In their researches, as already stated, the cases of clinical diphtheria were divided, on the strength of the bacteriologic examination, into diphtheric and non-diphtheric. The diphtheric anginas and croups were subdivided into (1) pure diphtheric forms, in which the Loeffler bacillus was present in a pure or almost pure condition; (2) diphtheric forms with microbic associations. The latter associations may vary. At one time there is present a small diplococcus, the coccus of Brisou; at another time a streptococcus; at another time a staphylococcus. In a few words, the same germs that are found in non-diphtheric forms may be associated with the Loeffler bacillus in real diphtherias.

The following table, compiled from the results obtained by Martin in 1892, and by Chaillou and Martin in 1894, demonstrates clearly the effect of microbic associations. All these cases contained the Loeffler bacillus. Those designated as "pure diphtheric" contained the Loeffler bacillus in almost pure culture, the number of foreign germs being very small, if at all present. In those cases designated as coccus-angina or croup, the predominating foreign germ, beside the Loeffler bacillus, was a small diplococcus. It will be observed that the percentage-mortality in this group is much less than in the group of pure diphtheric affections. In other words, the presence of a large number of cocci of this kind tends to counteract the effect of the Loeffler bacillus. In the third group are included those cases in which, in addition to the Loeffler bacillus,

streptococci or staphylococci predominate. Here it will be noticed that the percentage-mortality is much greater than in the pure diphtheric forms. The streptococci and staphylococci, therefore, either increase the pathogenic powers of the Loeffler bacillus directly, or by their own products give rise to additional intoxication, and, therefore, increased mortality:

	No. of cases.	No. of deaths.	Per ct.	Per ct. both anginas and croups.
Anginas:				
Pure diphtheric	96	38	40	.....
Diphtheric with coccus	14	1	7	.....
Diphtheric with streptococci or staphylococci	29	26	90	.....
Croups:				
Pure diphtheric	67	44	66	**50.3**
Diphtheric with coccus	19	5	26	**18.2**
Diphtheric with streptococci or staphylococci	25	19	76	**83.3**

There are a number of other interesting points regarding the Loeffler bacillus, such as the presence of this germ in the throats of healthy children; its occurrence in fibrinous rhinitis; in wound-diphtherias; its persistence in the throat after recovery from diphtheria; its relation to the non-virulent pseudo-diphtheria-bacillus, etc. These facts, however, have but little significance, so far as the proof of the relation of the Loeffler bacillus to diphtheria is concerned, and I shall, therefore, avoid their discussion.

Summarizing briefly the leading points brought out in this paper, it will be seen, *first*, that the Loeffler bacillus is present in much more than 73 per cent. of real clinical diphtherias; *second*, that pure cultures introduced into animals reproduce

false membranes, paralyses, and other ill-effects observed in diphtheria; *third*, that the chemic products of the bacillus produce paralyses, diarrhea, intoxication, and death, completing the resemblance to the natural disease; *fourth*, that the mortality is vastly greater in those cases in which the Loeffler bacillus is present than in those from which it is absent; *fifth*, that the antitoxic serum, which possesses a specific action toward the Loeffler bacillus and its poison, reduces the mortality in those cases in which the Loeffler bacillus is present and is without effect in those from which it is absent.

It is this overwhelming evidence that fully justifies us in stating that whenever the Loeffler bacillus is found in a disease it is diphtheria. It was with genuine pleasure that Loeffler could make the definite announcement at Budapest last year, ten years after his pioneer work of 1884, that "The cause of diphtheria is the diphtheria-bacillus."

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